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An Undescribed Variety of
Hereditary Edema.

BY

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PROFESSOR OF CLINICAL MEDICINE AND HYGIENE IN
THE OMAHA MEDICAL COLLEGE; PHYSICIAN TO
IMMANUEL HOSPITAL, ETC.

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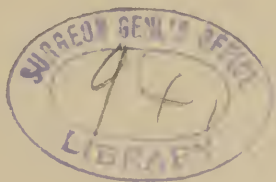
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AN UNDESCRIBED VARIETY OF
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BY W. F. MILROY, M. D.,

PROFESSOR OF CLINICAL MEDICINE AND HYGIENE
IN THE OMAHA MEDICAL COLLEGE; PHYSICIAN TO IMMANUEL HOSPITAL, ETC.

ON August 20, 1891, Mr. H. presented himself for examination for life insurance. He was an American, a clergyman, thirty-one years of age, six feet and half an inch in height, and weighed one hundred and seventy-eight pounds. His habits were the best, and he had never been sick in his life. With respect to longevity, his family history was excellent. Physical examination revealed nothing abnormal with regard to the thoracic or abdominal viscera. The applicant called my attention to his lower extremities. I found a condition of œdema involving the feet and extending up the legs to the knees. It was, and the patient states had always been, somewhat more marked in the left extremity than in the right. Upon inspection, the leg presented a slightly rosy hue, extending around its whole circumference and involving the whole extremity, gradually disappearing near the knee. When lightly pressed, the color disappeared, but returned quickly when the pressure was removed. Scattered thickly over this base were white spots about the size of a pea. These also were found over every part of the leg as far as the rosy color extended. This appearance of

* Read before the Society of the Alumni of Charity Hospital, June 1, 1892.

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the leg, according to the statement of the applicant, is constant. There were no varicose veins and no evidence of bad nutrition, nor was there any tendency to ulceration in any part of the leg. The circumference of the calf of the leg at its largest part was seventeen inches, and the smallest circumference of the ankle was fourteen inches. Deep pressure with the finger over the crest of the tibia, at a point near its middle, produced a depression which was distinctly apparent to both touch and sight ten minutes after the pressure was removed. This will convey an idea of the well-marked character of the œdema. The pitting on pressure was quite evident as far up as the tubercle of the tibia, but not over the patella or above it. Mr. H. stated that this œdematous enlargement had existed from birth. As he had grown in stature, the œdematous parts had grown so as to preserve the same size relative to the remainder of the body. It had always been free from pain, showed no disposition to ulcerate, and, in short, had never given him the least inconvenience. In the evening, if he had been on his feet a good deal during the day, the swelling seemed somewhat greater than in the morning, the skin appearing rather tense.

The applicant stated that this enlargement of the extremities was a family characteristic which he had inherited from his mother. Fortunately for the purposes of this study, the family of Mr. H.'s mother is one which has been long in America, and has been productive in New England. In 1883 a member of the family published a neat volume, giving the family history in America for a period of two hundred and fifty years. It should be remarked, however, that the peculiarity now under discussion seems to have entered the family by marriage about 1768. With the aid of this volume and the assistance of members of the family still living, I am able to offer the facts which I present, feeling that they are thoroughly reliable, though not at every point as complete as could be desired. For convenience I present, in graphic form, a summary of the family history, indicating in which individuals the œdema has occurred:

GENEALOGICAL TABLE SHOWING HEREDITARY OEDEMA IN THE FAMILY OF W.

I.	II.	III.	IV.	V.	VI.
		1. <i>James</i> . Unknown.			
		2. <i>Lydia</i> . One enlarged leg.	{ Six children. Three have each one enlarged foot.	{ Eleven children. Two have each one enlarged foot.	
		3. <i>Sarah</i> . Normal.	{ Eight children. One enlarged foot.	{ Nine children. All normal.	
		4. <i>Martha</i> . One leg enlarged.			
		5. <i>Olive</i> . Normal.	{ Five children. One enlarged leg.	{ Nine children. One has both legs enlarged; one has one foot enlarged.	
A relative of Mrs. W. had one en- larged leg.	{ Joseph W., both legs enlarged.	6. <i>Charity</i> . Both legs enlarged.	{ Four children. One enlarged leg.	{ Four children. One enlarged foot.	{ Six children. One has one foot en- larged; one has both feet enlarged.
		7. <i>Sally</i> . One foot and ankle enlarged.	{ Three children. One enlarged foot.	{ Two children. Normal.	
		8. <i>Mary</i> . Unknown.			
		9. <i>Julia</i> . One foot and leg enlarged.	{ Four children. One (the applicant), both legs enlarged.	{ Thirteen children. Normal.	{ Two children. Normal.

First Generation.—In 1768 Benjamin W. married Olive S. They were both physically normal, but a near relative (probably a sister) of Mrs. W. had an enlarged leg.

Second Generation.—Joseph W., son of Benjamin, was born in 1784, and died, at the age of seventy-eight years, of typhoid fever. He had both legs enormously enlarged.

Third Generation.—Joseph was twice married and had nine children, as follows:

1. James died at the age of four years, and no information has been able to be obtained in regard to him.

2. Lydia is still living at the age of eighty-two. She has one leg enlarged.

3. Sarah is also living, aged eighty. Her extremities are normal.

4. Twin birth. Martha, who died in infancy, had one leg enlarged. Olive died of "jungle fever" in India at the age of thirty-eight. Both of her extremities were normal.

5. Clarity is living at the age of seventy-five. She was born with one enlarged foot. When between twenty and thirty years of age she was thrown from a carriage, sustaining an injury in the sound leg. The injury was recovered from without special difficulty, but the leg gradually enlarged from that time until it reached enormous proportions. It has never given her the slightest inconvenience. She has through all her life enjoyed excellent health, and her extraordinary activity has always been a source of wonder to her friends.

6. Sally is living, aged seventy-three. She has one enlarged foot and ankle.

7. Mary died when a young child, and no information has been obtained in regard to her.

8. Julia is living at the age of sixty-six. Both extremities were normal until she was twelve years old. At that time one ankle had the appearance of having been sprained, though she was not aware of having thus injured it. For several weeks she could not walk on account of the distress in this ankle. The lameness was recovered from, though the swelling never disappeared, but, on the contrary, increased as she grew until it involved the foot and leg. It has never caused her any incon-

venience since the time mentioned, when she was twelve years of age. The other leg has remained normal.

Fourth Generation.—Lydia, the second daughter, had six children. Of these, the three daughters are normal. The three sons have each one foot somewhat enlarged.

Sarah has had eight children, of whom three are living. They were all normal with the exception of one son, who has a large foot.

Olive has had five children, of whom the youngest has one enlarged leg, the remainder being normal.

Charity has four children. Three of these are normal. The other has one enlarged leg.

Sally has two daughters and a son, the former being normal. The son had one enlarged foot. When he reached maturity his testicles began to enlarge, and this progressed to such a degree that he had one of them removed. As the enlargement of the testicles increased, that of the foot diminished until it was reduced to normal size, and it has since remained normal.

Julia had three children by her first husband, all of whom are normal. By her second husband she has one son (the applicant), with both legs and feet greatly enlarged.

Fifth Generation.—Of the descendants of Lydia, there are in this generation eleven children, of whom nine are normal. The remaining two, a son and a daughter, have each an enlarged foot.

Sarah has nine grandchildren, all normal.

Olive has nine grandchildren. A son of her eldest daughter has both legs enlarged, and a son of her eldest son has one foot enlarged. The others are normal.

Charity has three grandsons and one granddaughter. One of the sons has one enlarged foot. The remainder are normal.

Sally has two grandchildren, both normal. One of these is a son of the individual who had the testicle removed, as already referred to.

Julia has had thirteen grandchildren, all normal.

Sixth Generation.—Of the three grandsons of Charity mentioned, the eldest has three children, all normal. The youngest has also three children, of whom the eldest, a son, has one en-

larged foot; and the youngest, a daughter, has both feet enlarged.

Of the descendants of Julia, there are in this generation two children, both normal.

It thus appears that in the six generations of the family, comprising ninety-seven individuals, there have been twenty-two cases of this deformity, or about twenty-three per cent. of the whole number. Of the twenty-two cases, twelve were males, seven females, and three unknown, appearing to show that it is rather more common among the males than females of the family. In the later generations the percentage of cases is about as large as in the earlier, but there is a decided decrease in the extent of the œdema in most of them.

Atavism is frequently apparent in the development of the family peculiarity. I have not been able to learn that treatment has been undertaken for the cure of the affection in any case.

The invariable characteristics of the disorder have been : (1) Congenital origin with a steady growth corresponding to the normal growth of the body until adult size is attained ; (2) the limitation of the œdema to one or both lower extremities, the area involved varying ; (3) permanence of the œdema ; and (4) entire absence of constitutional symptoms, or local symptoms aside from those described.

Three exceptions to the usual course appear. The first of these is the case of Charity in the third generation. Having been born with one enlarged foot, its growth was characterized by the usual phenomena until she reached adult age. When above twenty years old she was thrown from a carriage, sustaining an injury in the sound leg. The immediate effects of the injury passed away within a reasonable time, but from this date the leg began to enlarge and continued to do so until it had attained enormous size, but,

at the same time, in no wise interfering with the health or activity of the individual.

The second exception is the case of Julia, also in the third generation. At birth and until she was twelve years of age her extremities were normal. Then, being unaware of having sustained any injury, one of her ankles developed the appearance of having been sprained. The usual signs of a sprain, including pain, tenderness, and swelling, were present to such a degree as to disable her for a number of weeks. Gradually all of the symptoms subsided with the exception of the swelling, and this increased and extended until it involved the foot and leg. It still remains, but never again has it given her any inconvenience.

The third exception, and the most remarkable, is that of a male in the fourth generation. Born with one enlarged foot, this grew in the usual manner until he arrived at maturity. Enlargement of the testicles then began and continued until they were so large that it was thought best to remove one of them, and this was done. As the enlargement of the testicles progressed, the abnormal size of the foot diminished until it became normal, and the enlargement has never returned. Unfortunately, the surgeon is dead who performed the castration, and I have been unable to obtain satisfactory information in regard to this most remarkable case. It is a question whether the enlargement of the testicle bore any particular relation to the family peculiarity, this not having occurred, so far as I am aware, in any other member of the family. But the fact remains that no other instance is known in which the œdema disappeared even temporarily.

The newness of the city and consequent dearth of medical libraries in Omaha is a serious obstacle in the way of the study of pathological and other questions here, and inasmuch as the literature at my command furnished no aid

to an understanding of this case, I wrote an incomplete account of it to Professor Francis Delafield, of New York, and also to Professor William H. Welch, of Baltimore, and I shall take the liberty to quote from these eminent authorities. In his reply Professor Welch says: "The case described in your letter is of extreme interest, and I do not know of one altogether like it recorded in literature. I should be inclined to put it in the category of angeio-neurotic œdemas. The congenital character of the affection and the existence of a similar condition in other members of the family, and the absence of any of the ordinary causes of œdema, speak for this view." Professor Delafield, whose reply was delayed for some time, says: "I have put off answering your letter of August 11th until this late date with the hope that I might be able to give you some information concerning your very interesting case of dropsy. I have found no reports of identical cases." He offered no suggestion as to the nature of the disorder.

I am indebted to Professor Welch for reference to a paper by Professor William Osler upon the subject of Angeio-neurotic Œdema. This was published in the *American Journal of the Medical Sciences* in April, 1888. Professor Welch also stated that he had shown my account of the case to Professor Osler, who concurred in the opinion that the case is one of angeio-neurotic œdema.

Angeio-neurotic œdema is a form of disease which is not so much as mentioned in any text-book or encyclopædia that I have been able to find in Omaha. Most of my information upon the subject I have obtained from the paper of Professor Osler already referred to, which contains, besides an account of his own cases, references to the very limited literature of the subject. A sufficient number of cases have been reported by different writers to show that it is not very uncommon.

Professor Osler describes the attack in one of his cases, that of Mrs. H., as follows:

“As long as she can remember she has been subject to attacks of transient swelling in various parts—hands or fingers, knee-caps, elbows, buttocks, arm or thigh in fleshy parts, face, or more often the lips alone. The fingers have been so swollen that it was impossible to move them, and once the ring finger was so greatly enlarged that the ring had to be filed off to prevent gangrene. The under lip has been swollen to such a degree that the mouth could not be opened and milk had to be poured in from above. A slight redness or itching of the part is first noticed, or a sensation of heat: the redness is not always present. The effusion may take place with great rapidity. She often has red spots on various parts of the skin or irregular lines of redness without any swelling. The duration varies from one to four days. There is not much itching, particularly when the swelling is great, but a sense of distention and stiffness. When fully *out* it does not pit, but does so when going down. The attack may come on when she is feeling quite well, or there may be slight indisposition. In all the severer ones there is abdominal pain, described as colic, with nausea and often vomiting. There is sometimes headache: no fever. The attacks have no relation to the menstrual flow. She rarely passes two weeks without an attack. She does not think that food has any influence on her case.”

This case is related as giving a fair idea of the character of the disorder, and Dr. Osler states that a review of the literature shows that all of the cases, in respect to their symptoms and course, are very similar. The hereditary tendency Osler found mentioned by three observers, and it was very marked in the family studied by himself. The most distressing symptom, in most of the cases, is the intestinal colic, which is so severe as to demand the administration of morphine.

Urticaria, which is a skin disease of neurotic origin, has

been so often found to precede or accompany the attacks of œdema that it is evident there is a close relationship between them. In speaking of the case to Dr. Gifford, he called my attention to the fact that there are certain subjects in whom an œdematous condition of the eyelids occurs without congestion. These attacks are transient, and are provoked by a more or less severe use of the eyes.

Quinke is the author of the term "angeio-neurotic œdema," basing the name upon the theory that the disease is a vaso-motor neurosis by means of which the permeability of the vessels is suddenly increased. However, in his letter, to which I have referred, Professor Welch says: "As to the pathology of angeio-neurotic œdema we know nothing. Even our knowledge of the physiology of the vaso-motor nerves does not explain how they could be disordered so as to cause œdema."

When the subject was first brought to my notice it occurred to me, as a possible explanation, that there might be a congenital absence of valves from the veins of the part affected. I was not aware that such an abnormality had ever been described, and have not since been able to learn that it has been known to exist. If it did exist, I do not know that it would cause œdema, and, indeed, a more perfect knowledge of the family history brings to light certain facts that seem at first glance, at least, not readily to harmonize with this theory.

There is, in my judgment, no pathological condition with which we are acquainted to which the case which I have related corresponds in a greater degree than what is known as angeio-neurotic œdema. Nevertheless, in most of the fundamental characteristics they are dissimilar.

Professor Osler says: "Briefly summarized, the affection in the family which I have studied has the following characteristics:

“1. The occurrence of local swellings in various parts of the body, face, hands, arms, legs, genitals, buttocks, and throat. In one instance, possibly in two, death resulted from a sudden *œdema glottidis*.

“2. Associated with the œdema there is almost invariably gastro-intestinal disturbance, colic, nausea, vomiting, and sometimes diarrhœa.

“3. A strongly marked hereditary disposition, the disease having affected members of the family in five generations.”

On the contrary, and strongly in contrast with this disorder in the family which I have studied :

1. So far as known, in every case, with two exceptions only, the œdema was present at birth.

2. The location of the œdema has in every case been limited to one or both lower extremities.

3. The presence of the œdema is persistent, never having been known to disappear, temporarily or permanently, except in one instance.

4. It has never been attended by constitutional symptoms, barring the two possible exceptional cases in which its first appearance was subsequent to birth.

From these considerations it seems evident that the case under discussion is not one of angeio-neurotic œdema, nor would it seem probable from the history that any functional neurosis could be responsible for the œdema.

It is proper to say in this connection that the account of the case upon which Professor Welch based his suggestion as to diagnosis was too fragmentary to admit a fair judgment of it.

Inasmuch as we know nothing as to the pathology of angeio-neurotic œdema, it may be possible that a correct elucidation of its nature would show that the case in question belongs in the same category.

The nature of the primary influences which control the process of transudation is still the subject of dispute among pathologists. That the influence of the nervous system is important, at least in certain cases, is not denied. Nevertheless, we are still in so great ignorance of the matter that a discussion of it can give little result of value. In his work on *General Pathology* Paync remarks: "Dropsy of nervous origin is caused by paralysis of the vaso-motor nerves, causing hyperæmia, which, in combination with some obscure factor, leads to effusion." In the case which I have narrated the "obscure factor" appears to be very conspicuous. Whether or not the case is one of nervous œdema, it is offered that, with others, sufficient material may be accumulated to render possible an intelligent study of these unusual forms of œdema.



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